ELSEVIER

Cigarette Smoking and Risk of Bladder, Pancreas, Kidney, and Colorectal Cancers in Iowa

BRIAN C.-H. CHIU, PHD, CHARLES F. LYNCH, MD, PHD,
JAMES R. CERHAN, MD, PHD, AND KENNETH P. CANTOR, PHD

PURPOSE: Although there are numerous reports on the effects of cigarette smoking and cancer, they have infrequently compared risks at more than one cancer site after multivariate adjustment. We analyzed data from a population-based case-control study that included five anatomic sites to evaluate the association between cigarette smoking and each cancer site and to rank the associations by site.
METHODS: Study respondents included 1452 bladder, 406 kidney, 376 pancreatic, 685 colon, and 655 rectal cancer cases, as well as 2434 population controls. A self-administered questionnaire was used to collect information on cigarette smoking and other potential confounders including occupation, drinking water source, and dietary practices. Logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals (CIs), after adjustment for age, total energy intake, and other site- and sex-specific confounders.
RESULTS: In both sexes, cigarette smoking (ever vs. never) was associated with risk of bladder cancer (OR = 2.5; 95% CI, 2.0–3.1 for males; OR = 2.7; 2.0–3.6 for females) and pancreatic cancer (OR = 1.8; 1.2–2.8 for males; OR = 2.1; 1.4–3.1 for females). Cigarette smoking also increased the risk of kidney cancer among males (OR = 1.8; 1.3–2.7), and to a lesser degree, among females (OR = 1.2; 0.8–1.8). No association was found for colon or rectal cancer in either sex.
CONCLUSIONS: Cigarette smoking increased the risk of bladder, kidney, and pancreatic cancer in men and women. The rankings of multivariate-adjusted ORs from highest to lowest were bladder, pancreas, kidney, and colorectum, with little difference between men and women.
Ann Epidemiol 2001;11:28–37.

KEY WORDS: Cigarette Smoking, Neoplasms, Bladder, Kidney, Pancreas, Colon, Rectum.

INTRODUCTION

Cigarette smoking is the most important known, modifiable, risk factor for human health today. It has been estimated to be responsible for more than 30% of all cancer deaths in the United States (1). Smokers have overall cancer death rates two times greater than those of nonsmokers and heavier smokers have rates four times greater (2). Worldwide, it is estimated that 15% (1.1 million new cases per year) of all cancer cases are attributed to cigarette smoking, 25% in men and 4% in women (3).

Cigarette smoking is by far the most important cause of lung cancer, and also an important determinant of cancer risk for at least six other anatomical sites: oral cavity and pharynx, esophagus, larynx, pancreas, kidney, and urinary bladder (4). Many questions remain, however, including the degree to which the development of certain cancers is attributed to cigarette smoking and the magnitude of the relative risks at different sites (5, 6). Although a multisite comparison can be made in a prospective study, long follow-ups are generally required for relatively rare cancers, such as bladder, kidney, and pancreas, to yield the number of cases that can provide statistically stable estimates of risk. In that regard, case-control studies are more cost-effective, even though they can suffer from other concerns including unrepresentative choice of a control group, use of surrogate informants, and recall bias. Nonetheless, prior case-control studies, except three (6–8), have focused on only a single cancer site.

In this study, we analyzed data from a population-based case-control study of 3574 cancer cases (bladder, kidney, pancreas, colon, and rectum) and 2434 controls to evaluate the association between cigarette smoking and five different cancer sites. Because exposure information was collected at the same time, this large case-control study provides a

From the Department of Epidemiology, The University of Iowa College of Public Health, Iowa City, IA (B.C.-H.C., C.F.L., J.R.C.); and Occupational Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD (K.P.C.). Dr. Brian C.-H. Chiu current affiliation: Department of Preventive and Societal Medicine, University of Nebraska Medical Center, Omaha, NE.

Address reprint requests to: Dr. Brian C.-H. Chiu, Section on Epidemiology, Department of Preventive and Societal Medicine, University of Nebraska Medical Center, 984350 Nebraska Medical Center, Omaha, NE 68198–4350.

Received November 10, 1999; revised June 2, 2000; accepted June 28, 2000.

655 Avenue of the Americas, New York, NY 10010

1047-2797/01/$–see front matter
PII S1047-2797(00)00175-7

Selected Abbreviations and Acronyms

SEER = Surveillance, Epidemiology and End Results
HCFA = Health Care Financing Administration

unique opportunity to rank the associations by site for comparative purposes while adjusting for site- and sex-specific confounders. In addition, we were able to control for exposure to factors related to occupation, environment, and dietary practices which have been shown to confound smoking but have not been adequately adjusted for in most of the previous epidemiologic studies of smoking and cancer (4).

MATERIAL AND METHODS

Study Population

A population-based, multi-site case-control study was conducted in Iowa between 1986 and 1989. Detailed methods may be found elsewhere (9, 10). Briefly, eligible cases were residents of the state of Iowa, aged 40–85 years, newly diagnosed with histologically confirmed cancer of the bladder, kidney, pancreas, colon, or rectum, and without a previous diagnosis of a malignant neoplasm with the exception of basal and squamous cell carcinomas of the skin. Cases were identified by the State Health Registry of Iowa, which is part of the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program. Cases of both *in situ* and invasive bladder cancer (transitional cell carcinoma and papillary transitional cell carcinoma) were included because these cancers appear to share the same set of risk factors (11) and because of cancer surveillance problems in delineating *in situ* and invasive bladder cancer (12).

Kidney cancer cases were adenocarcinomas, with cancers of the renal pelvis excluded. Pancreatic and colorectal cancer cases were adenocarcinomas. Of the 4166 eligible cases, 3574 participated (85.8%). Respondents included 1452 bladder (84.8% response rate), 406 kidney (87.7% response rate), 376 pancreatic (87.6% response rate), 685 colon (85.5% response rate), and 655 rectal (86.1% response rate) cancer cases. Of the case respondents, 781 (21.9%) were proxies for subjects who had died ($n = 778$), were incompetent ($n = 1$), or unavailable ($n = 2$). The proportion of respondents who were proxies varied by cancer site, from 10.7% (bladder) to 85.6% (pancreas).

Controls were frequency matched to all cases by sex and five-year age groups, resulting in a matching ratio ranging from 1.7:1 for bladder cancer to approximately 6.5:1 for pancreatic cancer. Vital status was not a matching criterion; only living controls were selected. Controls under 65 years of age were selected randomly from computerized State of Iowa driver's license records, whereas controls aged 65 years and older were selected randomly from listings provided by the U.S. Health Care Financing Administration (HCFA). Field activities were carried out in 1986–1987 for all cancer sites and controls, and for additional controls and bladder cancer cases in 1988–1989. Of the 3035 eligible controls, 2434 participated (80.2%). On two occasions, a proxy responded for a living control who was incompetent.

Data Collection

After obtaining passive physician consent (for cases), a letter explaining the nature and purpose of the study was mailed to each identified case or next of kin and control. A telephone call followed to invite the subjects to participate through completion of a mail questionnaire. Some subjects elected to complete a full telephone interview. The questionnaire included information on demographics, education, and occupational history; weight and height; a detailed smoking history including use of cigarette, cigars, pipes, snuff, and chewing tobacco; a 55-item food frequency questionnaire that included beer, wine, and liquor consumption; past medical conditions; family history of cancer; and lifetime residential history with detailed fluid consumption information including intake of beverages containing tap water and other beverages. Subjects who expressed reluctance to complete the detailed questionnaire at the initial telephone contract or at any time afterwards were offered a 15-minute shortened telephone interview. This abbreviated interview included only questions on demographic information, residential history, tobacco use, usual job, and fluid consumption. Among participants, 5380 (90%) completed the mailed questionnaire, 232 (4%) completed the full-length telephone interview, and 396 (7%) completed the abbreviated interview.

Upon return, questionnaires were screened for complete responses to several key items, including cigarette smoking history, residential/water supply history, and fluid intake. Respondents who had not answered fully the questions related to smoking history or other key items were re-contacted by telephone.

Exposure Measures

Three measures of cigarette smoking were evaluated. "Current smoking status" was categorized into three levels: never smokers, former smokers, and current smokers. Never-smokers were those who replied negatively to the question about using any tobacco products for six months or longer. Current smokers were defined as those who had smoked cigarettes for a continuous period of six months or longer and were also smoking within two years preceding diagnosis. Former cigarette smokers were defined as those who had quit smoking two or more years prior to the time of diagnosis (cases) or prior to the return of the questionnaire (controls). Former

smokers and current smokers were further combined to form an "ever smokers" category.

"Usual consumption," a measure of intensity, was the reported usual number of cigarettes smoked per day. For analysis, the amount smoked per day was grouped into five categories (never smokers, ≤10, 11–20, 21–40, >40 cigarettes/day). "Total lifetime consumption" was estimated in terms of pack-years of cigarette smoking, calculated by dividing average cigarettes smoked per day by 20 and multiplying by the number of years smoked. This constituted a measure that combined intensity and duration. For the purposes of analysis, pack-years of smoking were grouped into four categories (never smokers, ≤20, 21–40, >40 pack-years). Both of these measures were based on cutpoints commonly used in previous studies.

Selection of potential confounding factors or risk factors for a given cancer site was dependent on review of the literature and the data that were collected in this study. These factors differed by sex and cancer sites.

Statistical Analysis

Non-dietary variables of interest were grouped into standard strata. Important dietary risk variables were categorized by quartiles based on the distribution of consumption among controls. All models with dietary factors were adjusted for total energy intake, either by including total energy as a covariate in the model (for analyses involving micronutrients and food groups) or by using the residual method for adjustment of macronutrients (13). The maximum likelihood estimate of the odds ratio (OR) (14) and the 95% confidence interval (CI) were used to evaluate the association between various measures of cigarette smoking and cancer risk, by individual cancer site.

Unconditional multiple logistic regression models were used to estimate the ORs for each of the five cancer sites while adjusting for site-specific and sex-specific potential confounders. All models included age (four strata: 40–54, 55–64, 65–74, 75–85) and total energy intake (five levels: <5347, 5347–6853, 6853–8762, >8762 KJ/day, missing). Three methods (forward, backward, and stepwise logistic regression) were used to select variables for the basic model. Since they yielded similar models and almost identical point estimates, we arbitrarily chose the model from forward stepwise logistic regression for use in this study. After obtaining the basic model, each parameter measuring cigarette exposure was independently forced into the model to yield the full model. When testing for a trend, the exposure measure was entered as a continuous variable into the model. Finally, for comparative purposes, two different parameters measuring cigarette smoking, namely: 1) lifetime smoking experience (ever versus never); and 2) current smoking status (never, former, and current), were used to rank order the ORs for each of five cancer sites. These two parameters were chosen because studies have shown that next of kin respondents, in general, correctly identify the user status for cigarette smoking but report less reliably on detailed questions such as number of cigarettes smoked per day and duration of smoking (15). Analyses were conducted using SAS (SAS Institute, Cary, NC) software programs. Reported *p*-values are two-sided.

RESULTS

Table 1 presents the distributions of different parameters measuring cigarette smoking for cancer cases and controls. There were 1406 bladder cancer cases (1089 males and 317 females); 387 kidney cancer cases (242 males and 145 females); 362 pancreatic cancer cases (188 males and 174 females); 655 colon cancer cases (317 males and 338 females); and 629 rectal cancer cases (362 males and 267 females), and 2336 population controls (1503 males and 833 females) with cigarette smoking information available for data analysis. Among ever smokers, males had a higher proportion of former smokers, whereas more females were current smokers.

Table 2 shows the multivariable-adjusted ORs for each cancer site according to four different parameters measuring cigarette smoking while controlling for other sex-specific factors. For bladder cancer, male and female ever-smokers of cigarettes showed a significantly elevated OR of 2.5 (2.0–3.1) and 2.7 (2.0–3.6), respectively, compared with never smokers. Male current smokers were at a greater risk (OR = 3.7; 2.8–4.9) than male former smokers (OR = 2.0; 1.6–2.6). Corresponding ORs for females were 3.7 (2.6–5.3) and 1.8 (1.2–2.6), respectively.

Risk of bladder cancer increased with increasing number of cigarettes smoked per day. However, there was a decline in the ORs for male smokers, but not female smokers, of more than 40 cigarettes per day. Duration of cigarette smoking was also associated with increased risk of bladder cancer in both sexes. However, point estimates were not materially changed among smokers with increasing years of cigarette smoking. The risk of developing bladder cancer increased significantly according to pack-years of smoking from 1.9 (1.4–2.5) in male smokers of less than 20 pack-years (compared to never smokers), to 2.3 (1.7–3.0) in male smokers of 21–40 pack-year, to 3.0 (2.3–3.9) in male smokers of 40 or more pack-years. Corresponding ORs for females were 1.7 (1.1–2.6), 3.0 (2.0–4.6), and 3.5 (2.4–5.2), respectively.

The risk of kidney cancer was significantly associated with ever cigarette smoking among males, but to a lesser degree, among females (Table 2). Male ever cigarette smokers experienced a significant 80% increased risk of kidney cancer (95% CI, 1.3–2.7) compared with never smokers. The ORs for male former smokers and current smokers were 1.7 (1.2–2.6) and 2.1 (1.3–3.2), respectively. Corresponding

TABLE 1. Smoking characteristics of cancer cases and population controls, Iowa, 1986–89

	Males						Females					
Smoking Habits	Controls	Bladder	Kidney	Pancreas	Colon	Rectum	Controls	Bladder	Kidney	Pancreas	Colon	Rectum
Total[a]	1503	1089	242	188	317	362	833	317	145	174	338	267
New smokers[b]	435 (29%)	139 (13%)	40 (17%)	31 (16%)	73 (23%)	85 (23%)	574 (69%)	149 (47%)	92 (63%)	91 (52%)	222 (66%)	184 (69%)
Ever smokers	1068 (71%)	950 (87%)	202 (83%)	157 (84%)	244 (77%)	277 (77%)	259 (31%)	168 (53%)	53 (37%)	83 (48%)	116 (34%)	83 (31%)
Smoking status[c]												
Former	69%	55%	56%	54%	74%	67%	46%	33%	34%	37%	58%	59%
Current	31%	45%	44%	46%	26%	33%	54%	67%	66%	63%	42%	41%
Daily amount (cigarettes)[c,d]												
≤10	18%	14%	13%	18%	18%	19%	36%	26%	34%	28%	30%	34%
11–20	42%	41%	38%	31%	41%	43%	40%	44%	45%	37%	41%	49%
21–40	31%	36%	40%	42%	31%	30%	23%	26%	13%	24%	22%	13%
>40	8%	8%	8%	6%	9%	7%	1%	3%	8%	6%	2%	2%
Duration (years)[c,d]												
≤20	20%	12%	13%	16%	21%	19%	15%	8%	15%	8%	15%	22%
21–40	42%	37%	45%	41%	39%	43%	46%	38%	42%	43%	46%	47%
>40	38%	50%	39%	39%	38%	38%	38%	52%	43%	46%	38%	28%
Cumulative amount (pack-years)[c,d]												
≤20	27%	19%	20%	25%	28%	28%	36%	21%	36%	37%	37%	43%
21–40	25%	22%	25%	21%	28%	28%	30%	33%	25%	14%	28%	30%
>40	48%	59%	55%	54%	44%	44%	34%	45%	40%	48%	35%	27%

[a] Totals are limited to those subjects that provided information about cigarette smoking.
[b] Distributions among total subjects.
[c] Distributions among ever smokers.
[d] The percentages don't always sum to 100 because of missing data.

TABLE 2. Odds ratio (OR) and 95% confidence intervals (CI) for five cancer sites among males and females according to cigarette smoking characteristics, Iowa, 1986–89

	Males					Females				
	BL[a]	KI	PA	CO	RE	BL	KI	PA	CO	RE
Characteristics	OR[b] (CI)	OR[c] (CI)	OR[d] (CI)	OR[e] (CI)	OR[f] (CI)	OR[g] (CI)	OR[h] (CI)	OR[i] (CI)	OR[j] (CI)	OR[k] (CI)
Never smokers	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Smoking status										
Ever	2.5 (2.0–3.1)	1.8 (1.3–2.7)	1.8 (1.2–2.8)	1.3 (1.0–1.8)	1.3 (1.0–1.8)	2.7 (2.0–3.6)	1.2 (0.8–1.8)	2.1 (1.4–3.1)	1.3 (0.9–1.7)	1.0 (0.7–1.3)
Former	2.0 (1.6–2.6)	1.7 (1.2–2.6)	1.5 (1.0–2.4)	1.5 (1.1–2.0)	1.4 (1.0–1.8)	1.8 (1.2–2.6)	0.9 (0.5–1.6)	1.7 (1.0–2.9)	1.6 (1.1–2.2)	1.2 (0.8–1.8)
Current	3.7 (2.8–4.9)	2.1 (1.3–3.2)	2.5 (1.2–4.1)	1.0 (0.7–1.5)	1.3 (0.9–1.9)	3.7 (2.6–5.3)	1.4 (0.9–2.3)	2.4 (1.5–3.9)	1.0 (0.7–1.4)	0.7 (0.5–1.1)
Daily amount (cigarettes)										
⩽ 10	2.1 (1.5–2.8)	1.6 (1.0–2.8)	2.2 (1.2–3.9)	1.5 (1.0–2.4)	1.5 (1.0–2.2)	2.0 (1.3–3.0)	1.1 (0.6–2.0)	1.8 (1.0–3.1)	1.1 (0.7–1.6)	1.0 (0.6–1.6)
11–20	2.5 (1.9–3.2)	1.8 (1.1–2.7)	1.3 (0.7–2.1)	1.3 (0.9–1.8)	1.3 (1.0–1.8)	2.9 (2.0–4.3)	1.4 (0.8–2.7)	1.8 (1.1–3.2)	1.3 (0.9–1.9)	1.2 (0.8–1.8)
21–40	2.8 (2.1–3.7)	2.1 (1.4–3.3)	2.3 (1.4–3.8)	1.3 (0.9–1.9)	1.2 (0.9–1.8)	3.1 (1.9–5.1)	0.6 (0.3–1.5)	2.2 (1.1–4.2)	1.2 (0.7–2.0)	0.5 (0.2–0.9)
> 40	2.1 (1.4–3.2)	1.5 (0.8–2.9)	1.4 (0.6–3.1)	1.3 (0.7–2.3)	1.2 (0.7–2.0)	5.9 (1.3–27.2)	7.7 (1.3–45.7)	8.9 (1.8–43.5)	1.5 (0.2–9.9)	1.5 (0.2–9.7)
Duration (years)										
⩽ 20	1.5 (1.1–2.1)	1.2 (0.7–2.1)	1.5 (0.8–2.8)	1.5 (1.0–2.3)	1.2 (0.8–1.8)	1.5 (0.8–3.0)	1.1 (0.5–2.7)	1.5 (0.6–3.9)	1.3 (0.7–2.4)	1.4 (0.8–2.6)
21–40	1.5 (1.3–1.7)	1.4 (1.1–1.7)	1.3 (1.0–1.6)	1.1 (1.0–1.4)	1.1 (1.0–1.4)	1.5 (1.2–1.8)	0.9 (0.7–1.2)	1.5 (1.2–2.0)	1.1 (0.9–1.4)	0.9 (0.8–1.2)
> 40	1.5 (1.4–1.7)	1.3 (1.1–1.5)	1.2 (1.0–1.5)	1.1 (1.0–1.2)	1.1 (1.0–1.2)	1.5 (1.3–1.7)	1.2 (1.0–1.5)	1.2 (1.0–1.5)	1.1 (0.9–1.2)	0.9 (0.8–1.1)
Cumulative amount (pack-years)										
⩽ 20	1.9 (1.4–2.5)	1.5 (0.9–2.4)	2.0 (1.2–3.4)	1.5 (1.0–2.2)	1.4 (1.0–2.0)	1.7 (1.1–2.6)	1.1 (0.6–2.0)	2.4 (1.4–4.0)	1.4 (0.9–2.1)	1.3 (0.8–2.0)
21–40	2.3 (1.7–3.0)	1.9 (1.2–3.0)	1.5 (0.9–2.6)	1.6 (1.1–2.3)	1.5 (1.1–2.1)	3.0 (2.0–4.6)	1.0 (0.5–1.9)	1.1 (0.5–2.3)	1.1 (0.7–1.8)	0.9 (0.6–1.5)
> 40	3.0 (2.3–3.9)	2.0 (1.4–3.1)	1.9 (1.2–3.0)	1.1 (0.8–1.6)	1.2 (0.9–1.7)	3.5 (2.4–5.2)	1.4 (0.8–2.6)	2.5 (1.5–4.3)	1.2 (0.8–1.9)	0.7 (0.4–1.1)

[a] BL: bladder cancer, KI: kidney cancer, PA: pancreatic cancer, CO: colon cancer, RE: rectal cancer.
[b] Adjusted for age, total energy, high risk occupation, vegetables, total THM, coffee, bladder infection, and number of first degree relatives with bladder cancer.
[c] Adjusted for age, total energy, farming, fruits, coffee, and quetelet at age 20.
[d] Adjusted for age, total energy, vegetables, coffee, pancreatitis, gallbladder disease, and number of first degree relatives with pancreatic cancer.
[e] Adjusted for age, total energy, farming, fiber, colitis, number of first degree relatives with large bowel cancers, and quetelet at age 20.
[f] Adjusted for age, total energy, marital status, meat, number of first degree relatives with large bowel cancers, and quetelet at age 20.
[g] Adjusted for age, total energy, marital status, vegetables, coffee, and bladder infection.
[h] Adjusted for age, total energy, education, vegetables, number of first degree relatives with kidney cancer, and quetelet at age 40.
[i] Adjusted for age, total energy, education, meat, coffee, pancreatitis, jaundice, and number of first degree relatives with pancreatic cancer.
[j] Adjusted for age, total energy, education, fiber, and number of first degree relatives with colon cancer.
[k] Adjusted for age, total energy, red meat, and colitis.

ORs for women were 0.9 (0.5–1.6) and 1.4 (0.9–2.3), respectively. The number of cigarettes smoked per day was significantly associated with kidney cancer in males, but not in females. However, the estimate for the highest group in females lacks precision due to small numbers (95% CI, 1.4–45.7). For duration of smoking, although no dose-response effect was found, there was a significant association with the risk of kidney cancer in males, but not in females. There was also a significant trend of risk with increasing pack-years of smoking in males, but not in females.

Table 2 also presents the risk of pancreatic cancer associated with cigarette smoking by sex. Strong associations for pancreatic cancer were seen for all four parameters measuring cigarette exposure in both sexes. Among males with pancreatic cancer, ever smokers showed a significantly increased OR of 1.8 (1.2–2.8), former smokers had an OR of 1.5 (1.0–2.4), and current smokers had an OR of 2.5 (1.5–4.1), compared with male never smokers. Among females, the risk of developing pancreatic cancer for ever, former, and current smokers, as compared with never smokers, were 2.1 (1.4–3.1), 1.7 (1.0–2.9), and 2.4 (1.5–3.9), respectively. Among males, the risk did not significantly increase with the number of cigarettes smoked per day, years smoked, or pack-years of smoking, although an elevated risk was noted among all exposed groups. Among females, number of cigarettes smoked per day was significantly associated with risk of pancreatic cancer with an apparent dose-response effect, but numbers of females in the highest category of the amount smoked per day were too small to produce stable risk estimates (95% CI, 1.8–43.5). Both smoking duration and pack-years of smoking were significantly associated with the risk of pancreatic cancer in women, but the dose-response pattern was irregular.

There was essentially no association between cigarette smoking and risk of colon and rectal cancers in both males and females (Table 2). The point estimates for all four parameters measuring cigarette smoking were slightly above unity for both colon and rectal cancers in males, and for colon cancer in females. However, no consistent trends were observed.

We stratified ever smokers into two subgroups (former smokers and current smokers) and evaluated the dose-response relationship with number of cigarettes smoked per day or pack-year of smoking (Table 3). For those sites that are associated with cigarette smoking in this study (i.e., bladder, kidney, and pancreas), the effect of dose with number of cigarettes smoked per day was more pronounced among current smokers than among former smokers. A leveling-off of ORs with increasing smoking exposure appeared most clear among male former smokers. The dose-response effect with pack-years of smoking became less apparent after stratifying ever smokers according to current smoking status.

Figure 1 shows rank orders of the adjusted ORs for the five cancer sites by smoking status and sex. Among male current smokers, compared to never smokers, the OR for bladder cancer ranked highest, followed by the ORs for cancers of the pancreas, kidney, rectum, and colon. Among female current smokers, we found an analogous pattern. For former smokers, the rank order was less consistent between males and females and differed somewhat from that seen in current smokers. Among male former smokers, the ORs for bladder cancer ranked highest, followed by cancers of the kidney, pancreas, colon and rectum. For female former smokers, the rank ordering of ORs from highest to lowest were bladder, pancreas, colon, rectum, and kidney. The differing rank order of these cancers in females might be due to small numbers, especially for kidney cancer (Table 1).

DISCUSSION

Study findings support the association between cigarette smoking and bladder cancer, irrespective of gender. Both males and females who had ever smoked cigarettes had a significant 150% excess risk of bladder cancer. Our findings are consistent with previous studies (16–19). This study also indicates that cigarette smoking is an important risk factor in the development of kidney cancer in males, but to a lesser degree, in females; the OR was 1.8 for males who had ever smoked. These results are in general agreement with the overall evidence from previous case-control studies (20–22). However, in contrast to previous studies (20, 21, 23), we observed a weaker association with kidney cancer among females than among males, and this may have been due to chance. This study also provides further evidence that cigarette smoking is an important risk factor in the development of pancreatic cancer. A significantly increased risk was seen in both males and females. The results are consisted with previous investigations (24–26). Finally, our findings of lack of substantial relationships between cigarette smoking and the risks of colon and rectal cancer are similar to some studies (6, 27–29), but not to others (30–32).

The dose-response associations for cancers of the bladder, kidney, and pancreas in males, based on the average number of cigarettes smoked per day, showed a leveling-off or decreasing risk for smokers of more than 40 cigarettes per day. This leveling-off of ORs has been observed in other studies of bladder cancer (16, 33, 34), kidney cancer (23, 35), and pancreatic cancer (25, 36). Different explanations have been suggested, including the existence of diseases related to smoking that occur earlier than cancer (37), imperfect comparability between cases and controls because of study design problems (38), and diuretic properties of alcoholic beverages (33). It is also possible that a higher proportion of heavier smokers, compared to moderate smokers, died due to other diseases more commonly attributed to smoking (e.g., lung cancer and atherosclerotic heart disease), and thus were not available to be diagnosed with these cancers.

TABLE 3. Odds ratio (OR) and 95% confidence intervals (CI) for five cancer sites among males and females according to cigarette smoking status, Iowa, 1986–89

	Males					Females				
	BL[a]	KI	PA	CO	RE	BL	KI	PA	CO	RE
Characteristics	OR[b] (CI)	OR[c] (CI)	OR[d] (CI)	OR[e] (CI)	OR[f] (CI)	OR[g] (CI)	OR[h] (CI)	OR[i] (CI)	OR[j] (CI)	OR[k] (CI)
Never smokers	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Former smokers										
Daily amount (cigarettes)										
⩽ 10	1.8 (1.3–2.6)	1.5 (0.8–2.8)	2.6 (1.4–4.8)	1.7 (1.1–2.8)	1.4 (0.9–2.1)	1.6 (0.9–2.7)	0.9 (0.4–1.9)	1.8 (0.9–3.6)	1.4 (0.8–2.2)	1.1 (0.6–2.0)
11–20	2.2 (1.6–2.9)	1.7 (1.1–2.8)	1.1 (0.6–2.0)	1.4 (1.0–2.1)	1.3 (0.9–1.9)	1.9 (1.0–3.4)	1.1 (0.5–2.8)	1.6 (0.7–3.6)	1.7 (1.0–2.9)	1.7 (1.0–3.0)
21–40	2.2 (1.6–3.0)	2.3 (1.4–3.7)	1.6 (0.9–3.0)	1.5 (1.0–2.3)	1.4 (0.9–2.0)	2.0 (0.8–4.6)	0.2 (0.1–2.1)	0.8 (0.2–3.1)	1.7 (0.8–3.6)	0.4 (0.1–1.3)
> 40	1.2 (0.8–2.0)	1.2 (0.6–2.7)	0.3 (0.1–1.3)	1.1 (0.6–2.2)	0.9 (0.5–1.8)	3.2 (0.6–17.2)	—	1.8 (0.2–18.7)	1.5 (0.2–9.5)	1.6 (0.3–10.2)
Cumulative amount (pack-years)										
⩽ 20	1.7 (1.3–2.3)	1.4 (0.8–2.3)	1.9 (1.1–3.4)	1.4 (1.0–2.0)	1.3 (0.9–1.9)	1.6 (0.9–2.7)	1.0 (0.5–2.1)	2.0 (1.1–3.7)	1.5 (0.9–2.4)	1.4 (0.9–2.3)
21–40	2.2 (1.6–3.0)	2.3 (1.4–3.9)	1.4 (0.8–2.7)	1.8 (1.2–2.8)	1.7 (1.1–2.5)	1.8 (0.9–3.6)	0.7 (0.2–2.3)	1.4 (0.5–3.5)	1.5 (0.8–2.7)	1.2 (0.6–2.4)
> 40	2.2 (1.6–2.9)	1.9 (1.2–3.2)	1.2 (0.7–2.1)	1.3 (0.9–1.9)	1.1 (0.7–1.6)	2.2 (1.1–4.5)	0.5 (0.1–2.4)	1.7 (0.6–4.4)	1.8 (0.9–3.4)	0.9 (0.4–2.0)
Current smokers										
Daily amount (cigarettes)										
⩽ 10	3.0 (1.8–5.0)	2.2 (0.9–5.1)	1.1 (0.3–3.6)	1.0 (0.4–2.5)	1.7 (0.9–3.3)	2.9 (1.6–5.3)	1.4 (0.6–3.3)	1.9 (0.8–4.5)	0.7 (0.3–1.5)	0.9 (0.4–1.9)
11–20	3.7 (2.6–5.2)	2.0 (1.1–3.5)	1.9 (0.9–3.8)	1.0 (0.6–1.8)	1.3 (0.8–2.0)	4.1 (2.5–6.6)	1.5 (0.8–2.8)	2.1 (1.1–4.2)	1.1 (0.6–1.8)	0.8 (0.4–1.5)
21–40	4.8 (3.3–7.0)	2.2 (1.2–4.0)	4.7 (2.4–9.1)	1.0 (0.5–1.7)	1.2 (0.7–1.9)	4.4 (2.5–7.7)	0.8 (0.3–2.0)	3.2 (1.5–6.7)	0.9 (0.5–1.8)	0.5 (0.2–1.2)
> 40	9.6 (4.8–19.4)	3.1 (1.1–9.1)	11.7 (3.8–36.1)	2.4 (0.8–7.0)	2.0 (0.8–5.6)	—	—	—	—	—
Cumulative amount (pack-years)										
⩽ 20	3.9 (2.1–7.1)	3.1 (1.6–8.1)	1.8 (0.5–7.0)	2.4 (1.0–5.6)	2.2 (1.0–4.8)	2.1 (1.0–4.5)	1.3 (0.5–3.2)	3.5 (1.6–8.0)	1.2 (0.6–2.5)	1.2 (0.5–2.5)
21–40	2.7 (1.7–4.3)	1.4 (0.7–2.9)	2.2 (1.0–5.0)	0.9 (0.4–1.9)	1.0 (0.5–1.9)	4.3 (2.6–7.1)	1.1 (0.5–2.4)	0.9 (0.3–2.7)	1.0 (0.5–1.8)	0.7 (0.4–1.5)
> 40	4.6 (3.4–6.3)	2.3 (1.4–3.9)	3.2 (1.8–5.6)	1.0 (0.6–1.6)	1.3 (0.9–2.0)	4.5 (2.8–7.1)	1.8 (0.9–3.3)	3.0 (1.6–5.3)	1.0 (0.6–1.7)	0.6 (0.3–1.1)

[a] BL: bladder cancer, KI: kidney cancer, PA: pancreatic cancer, CO: colon cancer, RE: rectal cancer.
[b] Adjusted for age, total energy, high risk occupation, vegetables, total THM, coffee, bladder infection, and number of first degree relatives with bladder cancer.
[c] Adjusted for age, total energy, farming, fruits, coffee, and quetelet at age 20.
[d] Adjusted for age, total energy, vegetables, coffee, pancreatitis, gallbladder disease, and number of first degree relatives with pancreatic cancer.
[e] Adjusted for age, total energy, farming, fiber, colitis, number of first degree relatives with large bowel cancers, and quetelet at age 20.
[f] Adjusted for age, total energy, marital status, meat, number of first degree relatives with large bowel cancers, and quetelet at age 20.
[g] Adjusted for age, total energy, marital status, vegetables, coffee, and bladder infection.
[h] Adjusted for age, total energy, education, vegetables, number of first degree relatives with kidney cancer, and quetelet at age 40.
[i] Adjusted for age, total energy, education, meat, coffee, pancreatitis, jaundice, and number of first degree relatives with pancreatic cancer.
[j] Adjusted for age, total energy, education, fiber, and number of first degree relatives with colon cancer.
[k] Adjusted for age, total energy, red meat, and colitis.

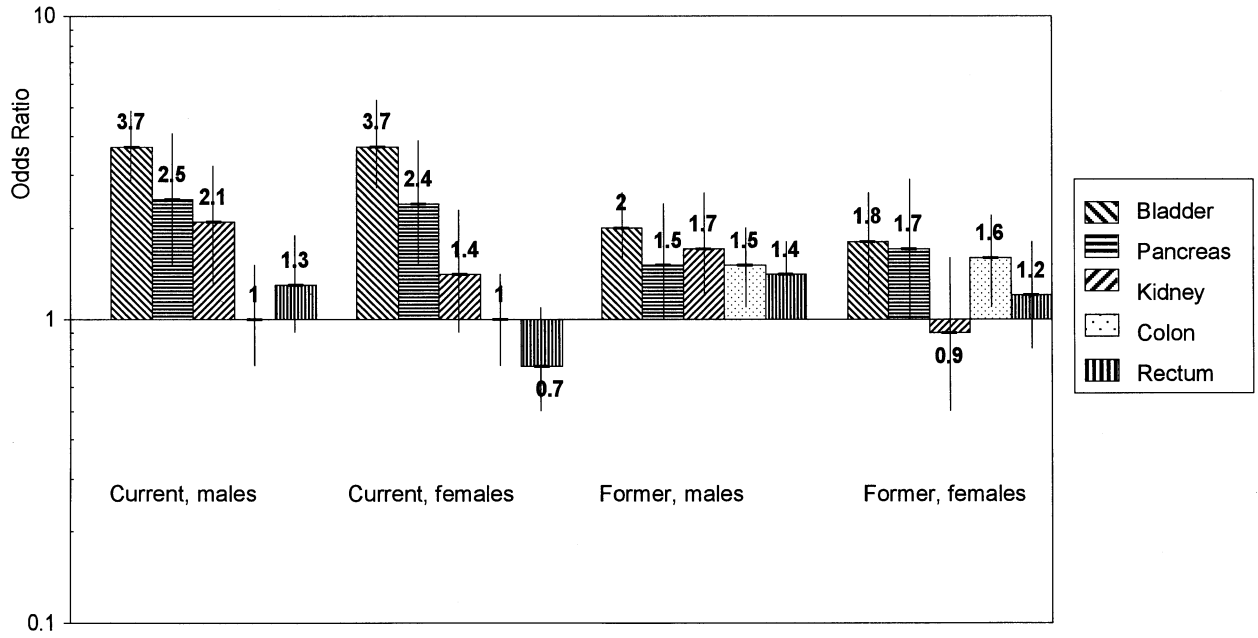

FIGURE 1. Rank order of the odds ratios for five cancer sites by current smoking status.

Finally, the leveling-off of risk could results from an uncontrolled confounding effect of smoking status. This appears to be at least a partial explanation for our findings because after stratifying subjects by current smoking status, we observed a leveling-off of ORs only in former smokers (most clear among male former smokers), not in current smokers.

In the present study, no clear pattern of risk with smoking duration was found for either men or women regardless of cancer site. It is possible that we may not have adequately assessed the effect of duration since controls were frequency-matched to cases on age. Most smokers begin smoking over a relatively narrow age range (roughly ages 14 to 21 years) and analyses of the association between duration of smoking and cancer risk may be confounded by this (4). We also included age in our statistical models which may have affected further our ability to evaluate the effect of smoking duration.

Our findings from rank ordering the ORs showed very similar rankings between former smokers and current smokers, although the magnitudes of effect differed. These findings express a need to explore explanations as to why cigarette smoking is more strongly related to one anatomic site than to others. First, it is possible that such modifiable risk factors as physical activity, body mass index, alcohol consumption, coffee consumption, and various dietary factors may act in concert with tobacco. This is especially true for cancers of the digestive tract. It is possible that the potential protective effect of certain dietary factors diminishes the carcinogenic effect of cigarette smoke.

Second, the relative risk of developing a tobacco-related cancer depends largely on the susceptibility and duration of contact of specific sites to various concentrations of certain smoking constituents and their metabolites (5). Organs such as the pancreas, kidney, and bladder are affected by certain tobacco compounds after they are metabolized in the liver or in the target organs and before they are excreted via the urinary tract (4, 5). Because urine stays longer in the bladder than in the kidney, this may explain why risks for kidney cancer are well below those found for bladder cancer. In addition, because the urothelium of the bladder is exposed to the same carcinogens in the urine as the tubular linings of the kidney which give rise to renal cell carcinoma, it remains possible that the tubular cells are less sensitive to these carcinogens (39).

Third, differences in rates of formation of carcinogen-DNA adducts may be important determinants in organ or tissue susceptibility to carcinogenic activity. For example, polycyclic aromatic hydrocarbons (e.g., benzo[a]pyrene) constitute by far the largest groups of carcinogens in tobacco smoke (40). These compounds are procarcinogens that require metabolic activation before they can exert their cytotoxic, mutagenic, and carcinogenic effects (41). Tissues with epithelial cells (e.g., oral cavity, lung, and bladder) have a slightly higher affinity for activating the procarcinogens, as measured by binding of benzo[a]pyrene to DNA. They also convert the primary benzo[a]pyrene metabolites into non-toxic, water excretable metabolites less efficiently than organs such as liver and colon (41). Fourth, genetic determinants may also affect organ or tissue susceptibility. Any or all of these explanations may account for differences in the rank ordering of ORs in this study.

In a case-control study, selection, non-response, and in-

formation biases may lead to spurious results. It is unlikely that selection bias played a significant role. Cases were identified through a high quality, population-based registry. The population-based control group was randomly selected from the general population of Iowa using the State of Iowa automobile driver's license list for those aged 40 to 64 years and rosters of the HCFA for those aged 65 to 84 years. Both of these are unbiased sampling frames and have been used successfully in selecting controls in other studies (42, 43). Non-response bias should not be a concern in the present study because of the high response rates for all cases (85.8%) and controls (80.2%). However, some information obtained from proxy respondents may have introduced bias. We have evaluated the effect of proxy respondents in the present study for each cancer site and found that age-adjusted OR among proxy respondents were in general greater than the corresponding ORs among live respondents for all five cancer sites. However, directions of association were consistent regardless of inclusion or exclusion of proxy respondents (44).

The major strength of the present study was its ability to provide for the simultaneous description and analysis of the overall pattern of risk for five different cancer sites. Exposure information was collected at the same time offering a unique opportunity to rank order the ORs for each of five cancer sites for comparative purposes. Another major strength was our ability to make adequate adjustment for exposure to potential confounders relating to occupation, environment, and dietary practices. Other strengths of this study included: 1) high response rates (80% or better, from all case series and from controls); 2) inclusion of newly diagnosed, histologically confirmed cases of five cancer sites that occurred in definite time periods in a single geographic area; and 3) a randomly selected population group control representative of the population at large.

In summary, cigarette smoking significantly increased the risk of bladder cancer and pancreatic cancer in both sexes. Cigarette smoking also increased the risk of kidney cancer among males, but to a lesser degree, among females. There was no association between cigarette smoking and colon or rectal cancer in either sex. The findings showed the rankings of multivariate-adjusted ORs from highest to lowest as bladder, pancreas, kidney, colon, and rectum, with little difference between men and women.

Support: This research was supported in part by National Cancer Institute research contracts (NCI-NO1-CP-51026 and NCI-N01-CP-85614) and by a Public Health Service Preventive Oncology Academic Award (K07 CA01181). We thank Kathleen McKeen, Dan Olson, Carmen Piruccello, and Christina Kerby for their technical assistance.

REFERENCES

1. International Agency for Research on Cancer (IARC). Tobacco: A Major International Health Hazard. Lyon: IARC; 1986.
2. Ernster VL. Trends in smoking, cancer risk, and cigarette promotion. Cancer. 1988;62:1702–1712.
3. Parkin DM, Pisani P, Lopez AD, Masuyer E. At least one in seven cases of cancer is caused by smoking. Global estimates for 1985. Int J Cancer. 1994;59:494–504.
4. Baron JA, Rohan TE. Tobacco. In: Schottenfeld D, Fraumeni JF Jr, eds. Cancer Epidemiology and Prevention. 2nd ed. New York: Oxford University Press; 1996:269–289.
5. Wynder EL, Hoffmann D. Tobacco. In: Schottenfeld D, Fraumeni JF Jr, eds. Cancer Epidemiology and Prevention. Philadelphia, PA: Saunders; 1982:277–292.
6. Siemiatycki J, Krewski D, Franco E, Kaiserman M. Associations between cigarette smoking and each of 21 types of cancer: A multi-site case-control study. Int J Epidemiol. 1995;24:504–514.
7. Choi SY, Kahyo H. Effect of cigarette smoking and alcohol consumption in the etiology of cancer in the digestive tract. Int J Cancer. 1991;49:381–386.
8. Murata M, Takayama K, Choi BCK, Pak AWP. A nested case-control study on alcohol drinking, tobacco smoking, and cancer. Cancer Detect Prev. 1996;20:557–565.
9. Cantor KP, Lynch CF, Hildesheim ME, Dosemeci M, Lubin J, Alavanja M, et al. Drinking water source and chlorination byproducts. I. Risk of bladder cancer. Epidemiology. 1998;9:21–28.
10. Chiu C-H. Cigarette Smoking and Selected Cancers in Iowa. Iowa City: The University of Iowa, Department of Preventive Medicine and Environmental Health; 1997.
11. Sturgeon SR, Hartge P, Silverman DT, Kantor AF, Linehan WM, Lynch CF, et al. Associations between bladder cancer risk and tumor stage and grade at diagnosis. Epidemiology. 1994;5:218–225.
12. Hankey BF, Edwards BK, Ries LA, Percy CL, Shambaugh E. Problems in cancer surveillance: Delineating in situ and invasive bladder cancer. J Natl Cancer Inst. 1991;84:384–386.
13. Willett WC, Stampfer MJ. Total energy intake: Implications for epidemiologic analyses. Am J Epidemiol. 1986;124:17–27.
14. Cox DR. The Analysis of Binary Data. London: Methuen; 1970.
15. Hyland A, Cummings KM, Lynn WR, Corle D, Giffen CA. Effect of proxy-reported smoking status on population estimates of smoking prevalence. Am J Epidemiol. 1997;145:746–751.
16. Harris RE, Chen-Backlund J-Y, Wynder EL. Cancer of the urinary bladder in Blacks and Whites. Cancer. 1990;66:2673–2680.
17. Burns PB, Swanson GM. Risk of urinary bladder cancer among Blacks and Whites: The role of cigarette use and occupation. Cancer Causes Control. 1991;2:371–379.
18. Hartge P, Silverman D, Hoover R, Schairer C, Altman R, Austin D, et al. Changing cigarette habits and bladder cancer risk: A case-control study. J Natl Cancer Inst. 1987;78:1119–1125.
19. Hartge P, Silverman DT, Schairer C, Hoover RN. Smoking and bladder cancer risk in Blacks and Whites in the United States. Cancer Causes Control. 1993;4:391–394.
20. Kreiger N, Marrett LD, Dodds L, Hilditch S, Darlington GA. Risk factors for renal cell carcinoma: Results of a population-based case-control study. Cancer Causes Control. 1993;4:101–110.
21. McLaughlin JK, Lindblad P, Mellemgaard A, McCredia M, Mandel JS, Schlehofer B, et al. International renal-cell cancer study. I. Tobacco use. Int J Cancer. 1995;60:194–198.
22. Tavani A, Pregnolato A, Violante A, La Vecchia C, Negri E. Attributable risks for kidney cancer in northern Italy. Eur J Cancer Prev. 1997; 6:195–199.
23. Muscat JE, Hoffmann D, Wynder EL. The epidemiology of renal cell carcinoma: A second look. Cancer. 1995;75:2552–2557.
24. Partanen TJ, Vainio HU, Ojajarvi A, Kauppinen TP. Pancreas cancer, tobacco smoking and consumption of alcoholic beverages: A case-control study. Cancer Lett. 1997;116:27–32.
25. Silverman DT, Dunn JA, Hoover RN, Schiffman M, Lillemoe KD,

Schoenberg JB, et al. Cigarette smoking and pancreas cancer: A case-control study based on direct interviews. J Natl Cancer Inst. 1994; 86:1510–1516.

26. Muscat JE, Stellman SD, Hoffmann D, Wynder EL. Smoking and pancreatic cancer in men and women. Cancer Epidemiol Biomarkers Prev. 1997;6:15–19.
27. Sandler RS, Lyles CM, McAuliffe C, Woosley JT. Cigarette smoking, alcohol, and the risk of colorectal adenomas. Gastroenterology. 1993; 104:1445–1451.
28. Baron JA, Sandler RS, Haile RW, Mandel JS, Mott LA, Greenberg ER. Folate intake, alcohol consumption, cigarette smoking, and risk of colorectal adenomas. J Natl Cancer Inst. 1998;90:57–62.
29. Nyren O, Bergstrom R, Nystrom L, Engholm G, Ekbom A, Adami H, et al. Smoking and colorectal cancer: a 20-year follow-up study of Swedish construction workers. J Natl Cancer Inst. 1996;88:1302–1307.
30. Giovannucci E, Colditz GA, Stampfer MJ, Hunter D, Rosner D, Willett WC, et al. A prospective study of cigarette smoking and risk of colorectal adenoma and colorectal cancer in U.S. women. J Natl Cancer Inst. 1994;86:192–199.
31. Giovannucci E, Rimm EB, Stampfer MJ, Colditz GA, Ascherio A, Kearney J, et al. A prospective study of cigarette smoking and risk of colorectal adenoma and colorectal cancer in U.S. men. J Natl Cancer Inst. 1994;86;183–191.
32. Yamada K, Araki S, Tamura M, Sakai I, Takahashi Y, Kashihara H, et al. Case-control study of colorectal carcinoma in situ and cancer in relation to cigarette smoking and alcohol use (Japan). Cancer Causes Control. 1997;8:780–785.
33. Augustine A, Hebert JR, Kabat GC, Wynder EL. Bladder cancer in relation to cigarette smoking. Cancer Res. 1988;48:4405–4408.
34. Kunze E, Chang-Claude J, Frentzel-Beyme R. Life style and occupational risk factors for bladder cancer in Germany. Cancer. 1992; 69:1776–1790.
35. Ross RK, Paganini-Hill A, Landolph J, Gerkins V, Henderson BE. Analgesics, cigarette smoking, and other risk factors for cancer of the renal pelvis and ureter. Cancer Res. 1989;49:1045–1048.
36. Kalapothaki V, Tzonou A, Hsieh C-C, Toupadaki N, Karakatsani A, Trichopoulos D. Tobacco, ethanol, coffee, pancreatitis, diabetes mellitus, and cholelithiasis as risk factors for pancreatic carcinoma. Cancer Causes Control. 1993;4:375–382.
37. Thornton A, Lee P, Fry J. Differences between smokers, ex-smokers, passive smokers and non-smokers. J Clin Epidemiol. 1994;47:1143–1162.
38. Vineis P, Esteve J, Terracini B. Bladder cancer and smoking in males: Types of cigarettes, age at start, effect of stopping, and interaction with occupation. Int J Cancer. 1984;34:165–170.
39. Mellemgaard A, Engholm G, McLaughlin JK, Olsen JH. Risk factors for renal cell carcinoma in Denmark. Role of socioeconomic status, tobacco use, beverages, and family history. Cancer Causes Control. 1994;5:105–113.
40. Hoffmann D, Schmeltz I, Hecht SS, Wynder EL. Tobacco carcinogenesis. In: Gelboin HV, Tso POP, eds. Polycyclic Hydrocarbons and Cancer. v. 1. New York: Academic Press; 1978:85–117.
41. Autrup H. Metabolism of polycyclic aromatic hydrocarbons in human target tissues. In: Hoffmann D, Harris CC, eds. Mechanisms in Tobacco Carcinogenesis. Cold Spring Harbor Lab; 1986:259–271.
42. Lynch CF, Logsden-Sackett N, Edwards S, Cantor KP. The driver's license list as a population-based sampling frame in Iowa. Am J Public Health. 1994;84:469–472.
43. Hartge P, Cahill JI, West D, Hauck M, Austin D, Silverman D, et al. Design and methods in a multi-center case-control interview study. Am J Public Health. 1984;74:52–56.
44. Chiu BC-H, Lynch CF, Cantor KP. Cigarette smoking and cancer: Effect of proxy respondents on risk estimates. Am J Epidemiol. 1998; 147:S6.